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LETTER TO THE EDITOR

Neurotoxicity associated with dimethylsulfoxide-preserved hematopoietic progenitor cell infusion

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Dimethylsulfoxide (DMSO) is used as a cryoprotectant for long-term storage of hematopoietic progenitor cells from the marrow or blood.[1] Although DMSO is generally considered to be relatively innocuous, a variety of dose-dependent adverse effects have been associated with its infusion including nausea, vomiting, flushing, fever, chills, dyspnea, cardiac symptoms, transient hypertension or hypotension and anaphylaxis.[2–5] Isolated cases of encephalopathy and seizures have also been reported to be associated with the infusion of DMSO-cryopreserved hematopoietic stem cells.[6–9]

A 50-year-old woman with nodular-sclerosing Hodgkin's disease presented for high-dose chemotherapy and autotransplantation. The original disease had been treated with six cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), and relapse 3 years later had been treated with three cycles of dexamethasone, cytarabine, cisplatin (DHAP). Stem cells were collected by apheresis after mobilization with cyclophosphamide 120 mg/kg followed by 14 μg/kg/day G-CSF, which resulted in a harvest of 2.63×10^6 CD34+ cells/kg. The cells were cryopreserved in 10% DMSO (Edwards Lifesciences, Irvine, CA, USA) using a controlled-rate freezer (Cryomed, Thermo Scientific, Waltham, MA, USA) and stored at −150 °C (REVCO Ultima II, Thermo Scientific, Asheville, NC, USA). The final total volume cryopreserved was 540 ml in six bags, with approximately 9 g of DMSO per bag (0.15 g/kg DMSO per bag).

After carmustine, etoposide, cytarabine, melphalan (BEAM) high-dose conditioning, the patient received premedication with 50 mg diphenhydramine and 200 mg hydrocortisone before stem cell infusion. The bags were thawed in a 37 °C water bath and infused at a rate of 10 ml/min. After the infusion of the second bag, the patient developed skin pallor, loss of consciousness, mydriasis, trismus and respiratory arrest with no spontaneous respiration. The stem cell infusion was immediately stopped. A seizure was suspected and she was administered a 15 mg/kg loading dose of phenytoin. She recovered consciousness in less than an hour after assisted ventilation was started. Phenytoin was continued at a dose of 4.5 mg/kg i.v. per day for 5 days and then switched to oral maintenance therapy. Later in the day, the remaining cryopreserved stem cells were reinfused and no adverse effects were observed. These were not been washed to deplete DMSO.

Brain CT scan showed no abnormalities. Electroencephalogram showed diffuse abnormalities in the electric activity with irregular paroxysms of slow waves of generalized projection. On brain magnetic resonance imaging, a punctuate area of hyperintensity was seen in the right middle frontal lobe on diffusion-weighted imaging. Due to its small size, its clinical significance was unclear. It could have been the result of previous ischemia or a technical artifact. After engraftment on day +12, she developed pulmonary complications associated with respiratory syncytial virus and died on day +23. No other neurological adverse event occurred before her death.

As DMSO is usually not removed from the stem cell component before infusion, some adverse effects attributable to it can be seen occasionally. Some centers report a high incidence of toxicity related to the reinfusion of marrow or blood stem cells cryopreserved in DMSO, but these are generally mild. These include skin flushing, a variety of gastrointestinal and cardiopulmonary complaints and occasional anaphylactic reactions. These are usually treated symptomatically and resolved in a few hours.

Although headache has been reported, other neurologic complications are rare. Isolated cases of encephalopathy and seizures have been described following the i.v. administration of DMSO.[8,9] Bawens *et al.*[9] reported a patient who presented an episode of tonic–clonic seizure over a few minutes after the start of stem cell infusion and developed profound and sustained encephalopathy with coma after the second infusion.

Our patient developed profound but rapidly reversible depression of the central nervous system with respiratory arrest and a complex partial seizure after infusion of 18 g of DMSO (the equivalent of 0.3 g/kg) in 180 ml cryopreserved HPCs. She developed this severe complication despite an acceptable dose of DMSO reinfused at a rate generally considered safe. Other probable causes of seizures such as metabolic abnormalities, structural brain lesions and sepsis were ruled out.

In the absence of other causes, we attribute the reaction to DMSO toxicity. The pathophysiology of DMSO neurotoxicity remains unclear. While the toxic dose of DMSO for humans has not been determined, the severity of the toxic manifestation for the brain and other organs has been thought to be related to the amount of DMSO present in the graft or to the rate of its infusion. The maximal recommended dose of DMSO to be reinfused in one session is 1 g/kg of bodyweight or 10 ml/kg of a 10% DMSO cryopreserved solution. When the volume to be infused exceeds this limit, one approach is to divide the infusion into two or three aliquots given several hours or a day apart to reduce the amount of DMSO given to the patient at a given time. If toxicity is observed with an infusion, the stem cell product can be washed after thawing to deplete it of

DMSO. DMSO toxicity may also be idiosyncratic, and may thus be unpredictable and unavoidable.

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